REMARKS

Applicant thanks the Examiner, and the Examiner's superviser, Johann Richter, for the very productive interview of June 19, 2007. An interview summary follows.

Interview summary

A presentation was given as to how the Applicant believes the present claims are distinguished over Mezei et al., (US patent 5,451,408). Specifically, the Applicant pointed to sections of the Mezei et al., patent which taught or suggested that an optimal ratio of liposomally encapsulated to free fentanyl would be about 80-90% liposomally encapsulated to 10-20% free, and showed modeling data suggesting that, surprisingly, a ratio of about 3:2 would be an excellent ratio for use in the desired manner. Applicant brought forward the argument that Mezei et al., and the present invention, were directed at different problems, and thus required different solutions to those problems. Specifically, Mezei et al. was directed towards an opioid formulation suitable for pulmonary delivery, with the longest possible duration of action. Given that goal, Mezei et al. discovered that a liposomal formulation provided extended release, and long duration of action. Mezei et al. further disclosed that a fentanyl ratio of 80-90% encapsulated to 10-20% free drug provided an optimum balance of duration and onset of action.

Applicant brought forward the argument that the purpose of the presently claimed invention was different. The present invention is directed towards an opioid formulation suitable for pulmonary delivery, but instead of the longest possible duration of action, the inventors were seeking a formulation useful for self-administration of opioid, wherein a patient could titrate their opioid dose to effect. There are substantial challenges with self-administration of opioid, one of the most notable being that with many formulations, the peak effect of the opioid occurs much later than the administration. Thus, a patient

will take opioid until they feel the benefit, but will be subjected to a much higher, potentially toxic, dose, at a later point in time. This significant challenge was not addressed in Mezei et al., which shows, for example, at Table 1 examples 3 and 4, an administration of 15 minutes, and a Tmax for the opioid of 28 and 23.3 minutes, respectively.

Applicant showed graphs of the exemplified invention, as shown in Figure 20A of the patent, which showed that, with the taught and novel formulation, the maximum plasma concentration of opioid was very near, and in most cases within 80% of the end of dose concentration. Applicant also showed corresponding Tmax data suggesting that Tmax occurred very shortly after end of dose.

Applicant therefore submitted that claim 17, and claims dependent thereupon, were a novel, non-obvious, and patentably distinct selection of the general opioid formulations (i.e. a formulation containing liposomally encapsulated and free opioid) as taught in Mezei et al.

The Examiner agreed that claim 17 was novel over the prior art. The Examiner carefully reviewed Mezei et al., and suggested that a showing that the claimed compositions were different from the compositions taught in the prior art, or, in the absence of such showing, a showing of unexpected results, would overcome the obviousness rejection.

Also discussed was claim 48. The Examiner reviewed claim amendments to claim 48, and agreed, in principle, that an amendment to claim 48 that would describe Figure 18 adequately, and selected the specific opioids, should overcome the rejection of that claim.

Applicant agreed to review the raw data and lab notebooks from the time of Mezei et al., to determine whether the claimed compositions were different from the compositions taught in the prior art.

Further Remarks

Claims 1-28 have been cancelled. Claims 27-37 have been withdrawn due to a restriction requirement. Claim 48 has been amended to more clearly define the ambit of protection sought.

Claim Rejections – 35 USC 112

The Examiner has rejected claim 18 under 35 USC 112, first paragraph, as failing to comply with the written description requirement. Applicant has cancelled claim 18, rendering this objection moot.

The Examiner has rejected claim 48 under 35 USC 112, first paragraph, because the specification, while being enabling for an opioid formulation comprising either (1) fentanyl and liposomally encapsulated fentanyl or (2) the combination of (a) remifentanil, alfentanil, sufentanil or fentanyl and (b) methadone, wherein said formulation exhibits a pharmacokinetic profile substantially similar to that depicted in Figure 18, does not reasonably provide enablement for an opioid formulation comprising any two opioids and exhibiting a pharmacokinetic profile similar to that depicted in Figure 18.

Applicant respectfully traverses. Applicant believes that the ample examples from the specification enable an opioid formulation comprising any two opioids and exhibiting a pharmacokinetic profile substantially similar to that depicted in Figure 18. However, solely in an effort to advance prosecution, and by no means in acquiescence of the Examiner's rejection, Applicant has amended claim 48 to specify that the two opioids are (1) a rapid onset opioid and a sustained effect opioid; and (2) selected from a group

substantially similar to that described as enabled by the Examiner. Note that the Applicant has added morphine to the list of sustained effect opioids. Applicant respectfully submits that morphine is specifically enabled, and draws the Examiner's attention to figure 18, for example, which enables morphine.

The Examiner has rejected to claim 48, stating that claim 48 requires that the mixture of any two opioids exhibit a pharmacokinetic profile "substantially similar" to that depicted in Figure 18 of the instant application, and that the instant specification does not define or explain what is a substantially similar pharmacokinetic profile. The Examiner also rejects the claim as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, stating that the term "similar" is a relative term which renders the claim indefinite, the term "substantially" renders the claim vague and indefinite, and reference to figure 18 is vague and indefinite because it requires a reader to reference an outside figure.

Applicant has amended claim 48, removing the terms "substantially" and "similar", and defining the effect curve of figure 18 such that a combined pharmacokinetic profile of the opioids has a combined effect curve "providing a peak concentration at an effect site at between 10 and 30 minutes" and a sustained effect of a magnitude of at least 85% of said peak effect for at least two hours. The Examiner is kindly reminded that very similar claim language was presented in the interview of June 19, 2007, and the Examiner gave positive feedback, stating that, at first glance and in principle, it appeared to adequately describe figure 18 and overcome the rejection.

Claim Rejections - 35 USC 103

The Examiner has rejected claims 7-36 and 48 as being unpatentable over Mezei et al. Specifically, the Examiner has stated that the Applicants' claimed ratio of free fentanyl to liposomally encapsulated fentanyl merely represents a routine optimization in the

amounts of free fentanyl and liposomally encapsulated fentanyl. Regarding the combination of alfentanil and morphine and the relative amounts of these two opioids, the Examiner contends that the specification lacks any objective evidence demonstrating that the claimed combination in the claimed ratios and relative amounts demonstrates an unexpected property or result in comparison with other binary opioid combinations and/or different relative amounts of alfentanil and morphine.

Applicant has cancelled claims 7-28, rendering this rejection, with respect to those claims, moot.

With respect to claims 48 and 29-36, Applicant respectfully traverses. Applicant submits that amended claim 48 is unobvious in light of Mezei et al. In Mezei et al., the problem (or goal) was an extended release opioid formulation. The solution to that problem was a combination of a liposomally encapsulated opioid with a free opioid. The present invention has both a different problem, and a different solution. The present problem is the preparation of an opioid composition that allows a patient to self-administer, and self-dose, titrating to effect, through a pulmonary administration. That problem was not discussed, or even attempted to be resolved in Mezei et al. The solution, an opioid formulation comprising a rapid onset opioid and a sustained effect opioid, such that the ratio of the opioids is selected such that a combined pharmacokinetic profile has a combined effect curve providing a peak effect at between 10 and 30 minutes and a sustained effect of a magnitude of at least 85% of said peak effect for at least two hours, and wherein the rapid onset opioid is one of fentanyl, remifentanil, alfentanil and sufentanil and the sustained effect opioid is selected from morphine and methadone, is neither taught or suggested in Mezei et al. Applicant submits that the opioid compositions claimed in claim 48, and claims 29-36 dependent thereupon, are a useful and unobvious selection over that claimed in Mezei et al. There is no motivation in Mezei et al., to create a formulation useful for patient self-dosing and titration to effect.

Double Patenting

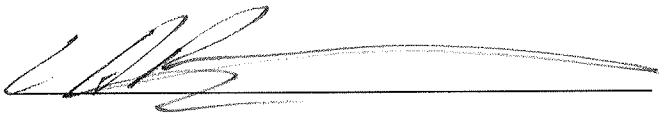
The Examiner has rejected claims 17-18 on the ground of nonstatutory obviousness-type double patenting. Applicant has cancelled claims 17 and 18, rendering this rejection moot.

The Examiner has provisionally rejected claims 17-21, 29-30 and 33 as being unpatentable over claims 7-8 and 10-11 of copending Application No. 10/927,145. Applicant has cancelled claims 17-21, rendering this objection with respect to those claims moot. Applicant has requested the rejection be held in abeyance until the claims of the instant application or those of copending application no. 10/927,145 are in a condition for allowance.

Conclusion

It is respectfully submitted that the present amendments and remarks herein are a complete response to all outstanding issues. Favorable consideration is respectfully requested. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully Submitted,
Steven Louis Shafer et al

By: 
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